

APPLICANT(S): WURTMAN, Richard  
SERIAL NO.: 09/363,748  
FILED: June 30, 1999  
Page 3

### **REMARKS**

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

#### **Status of Claims**

Claims 54-61 are pending in the application. Claims 54-61 have been rejected. Claims 54, 57-59, and 61 have been amended.

#### **Drawings**

In the Office Action, the Examiner alleged that the drawings accompanying the subject application are acceptable for examination purposes only, and that formal drawings will be required when the application is allowed.

In response, Applicants request permission to defer submission of formal drawings correcting these objections until the present application is allowed.

#### **Claim rejections under 35 U.S.C. § 112, first paragraph**

In the Office Action, the Examiner rejected claims 54 and 59 under 35 U.S.C. § 112, first paragraph, for containing the phrase "a derivative or metabolite thereof," which allegedly is not adequately supported in the written description.

In response, in order to expedite prosecution, amended claims 54 and 59 do not contain the phrase "a derivative or metabolite thereof." Dependent claims 58 and 61 have been corrected accordingly to maintain proper antecedence.

Accordingly, Applicants request withdrawal of the rejections.

#### **Claim rejections under 35 U.S.C. § 112, second paragraph**

The Examiner further rejected claims 54 and 59 under 35 U.S.C. § 112, second paragraph, for containing the terms "a brain," "a uridine," and "a cytidine," allegedly

APPLICANT(S): WURTMAN, Richard  
SERIAL NO.: 09/363,748  
FILED: June 30, 1999  
Page 4

implying the possibility of multiple brains in the subject and multiple uridine and cytidine compounds.

In response, in order to expedite prosecution, amended claims 54 and 59 do not contain the objected-to terms; rather, they read "the brain," "uridine," and "cytidine."

Accordingly, Applicants request withdrawal of the rejections.

The Examiner further rejected claims 54 and 59 under 35 U.S.C. § 112, second paragraph, for containing the allegedly incomplete term "a subject".

In response, in order to expedite prosecution, amended claims 54 and 59 contain the term "a subject in need thereof"; instead of "a subject."

Accordingly, Applicants request withdrawal of the rejections.

The Examiner further rejected claim 57 under 35 U.S.C. § 112, second paragraph, for containing the allegedly indefinite term "such as," and for containing the term "a uridine source," which allegedly reads on subject matter excluded by the specification.

In response, in order to expedite prosecution, amended claims 54 and 59 do not contain the terms "such as" or "a uridine source."

Accordingly, Applicants request withdrawal of the rejection.

The Examiner further rejected claims 58 and 61 under 35 U.S.C. § 112, second paragraph, for containing the term "a uridine-5'-phosphate," allegedly implying the possibility of multiple uridine-5'-phosphate compounds.

In response, in order to expedite prosecution, amended claims 54 and 59 do not contain the term "a uridine-5'-phosphate"; rather, they read "uridine-5'-phosphate."

Accordingly, Applicants request withdrawal of the rejections.

#### **Claim rejections under 35 U.S.C. § 102**

In the Office Action, the Examiner rejected claims 54, 56, and 58-61 under 35 U.S.C. § 102(b), as being anticipated by the Dawson reference, alleging that Dawson disclosed the administration of radiolabeled UMP to a mammalian host and the observation that radiolabeled CMP is found subsequently within the tissues of the host.

APPLICANT(S): WURTMAN, Richard  
SERIAL NO.: 09/363,748  
FILED: June 30, 1999  
Page 5

In response, Applicants traverse the rejection. Dawson did not disclose that administration of uridine raises cytidine levels in the brain. Dawson's alleged disclosure that administration of radioactive UMP to rats resulted in radioactive cytidine in the rats' brains reveals nothing about total brain cytidine levels. Dawson did not measure total cytidine levels in the brain, rather measuring only the appearance of  $^{14}\text{C}$ -labeled cytidine. Without knowledge of brain cytidine levels, it is clearly impossible to draw any conclusions about the effect of uridine administration on brain cytidine levels. The most that this finding shows is that uridine can be converted into cytidine in the brain. Dawson himself advanced this interpretation of his findings in the first paragraph following the abstract (page 31), stating,

"The results reported here indicate that such a conversion can indeed take place in the brain."

Thus, as admitted by Dawson, Dawson did not disclose that administration of uridine raises cytidine levels in the brain.

In addition, the alleged finding that uridine can be converted into cytidine in the brain provides no credible evidence that administration of uridine is effective to raise cytidine levels in the brain. Many cases are known in the art of enzymes that are saturated with their substrates at physiological concentrations of the substrates, so that adding more substrate will *not* increase the rate of product formation. For example, the rate of cholesterol biosynthesis is determined by the activity of the enzyme HMG-CoA (hydroxymethylglutaryl-CoA reductase) rather than by the amount of its substrate beta-hydroxy-methylglutaryl CoA ("Regulation of cholesterol biosynthesis" pp. 258-259 in: G.F. Gibbons, K.A. Mitropoulos and N.B. Myant, Biochemistry of Cholesterol, Elsevier, Amsterdam, 1982; copies of all references are attached). In addition, many enzymes are known in the art to be subject to feedback inhibition, in which the product of an enzyme inhibits the enzyme, thus keeping levels of the product from rising when more of its substrate is available; cytidine itself is involved in such inhibition (pp 75-76, Functional Design of Proteins, Chapter 3.3 from Lodish et al, Molecular Cell Biology, WH Freeman and Co, 2000). Thus, Dawson would not have been credible evidence to a person skilled in the art that uridine increases the rate of cytidine formation.

In addition, even if Dawson had shown that uridine administration increases the *rate of formation* of cytidine, that finding would not show that uridine administration increases

APPLICANT(S): WURTMAN, Richard  
SERIAL NO.: 09/363,748  
FILED: June 30, 1999  
Page 6

cytidine *levels*. The concentrations of many enzyme products in the body are subject to homeostatic control, which is not affected by the concentrations of substrates of the enzyme. For example, while administration of labeled cholesterol results in formation of labeled testosterone and estrogen (A. Zaffaroni, O. Hechter, and G. Pincus, "Adrenal conversion of C<sup>14</sup>-labeled cholesterol and acetate to adrenal cortical hormones", J Am Chem Soc 73: 1390-1391, 1951), *levels* of testosterone and estrogen are not affected by high cholesterol levels (Kato I et al, "Determinants of sex hormone levels in men as useful indices in hormone-related disorders," J Clin Epidemiol. 1992 Dec;45(12):1417-21; see abstract). Thus, Dawson's finding that administration of radioactive UMP results in formation of radioactive cytidine clearly provides no credible evidence that addition of uridine would raise cytidine levels in a subject.

Thus, Dawson (a) did not disclose and (b) provided no credible expectation to a person skilled in the art that uridine administration increases cytidine levels. Therefore, Dawson does not teach a method of increasing brain cytidine levels, comprising administering a uridine, as recited in the subject claims.

Accordingly, Applicants request withdrawal of the rejections.

#### **Claim rejections under 35 U.S.C. § 103**

In the Office Action, the Examiner rejected claims 54-61 under 35 U.S.C. § 103(a), as being unpatentable over Dawson in view of the von Borstel and Lehninger references. The Examiner alleged that Dawson disclosed the administration of radiolabeled UMP to a mammalian host and the observation that radiolabeled CMP is found subsequently within the tissues of the host. The Examiner admitted, however, that Dawson did not disclose administration of uridine or a uridine source orally or as a food component. The Examiner further alleged that von Borstel disclosed oral administration of uridine, UMP, and other uridine derivatives, that Lehninger disclosed conversion of uridine into cytidine in living cells, and that it would have been obvious to a person of average skill in the art to combine these references to orally administer uridine to a host in need thereof.

In response, Applicants traverse the rejection and agree that Dawson did not disclose administration of uridine or a uridine source orally or as a food component. As described

APPLICANT(S): WURTMAN, Richard  
SERIAL NO.: 09/363,748  
FILED: June 30, 1999  
Page 7

above, Dawson did not show that uridine administration increases cytidine levels. Similarly, for the reasons described above for the Dawson reference, Lehninger's disclosure that uridine can be converted to cytidine in cells would not have been credible evidence to a person skilled in the art that uridine administration increases cytidine levels. In addition, it was well known in the art that metabolic experiments performed in cells are often not predictive of results obtained in intact animals. Thus, neither Dawson nor Lehninger either (a) disclosed or (b) provided a credible expectation to a person skilled in the art that uridine administration increases cytidine levels. Therefore, these references do not teach a method of increasing brain cytidine levels, comprising administering a uridine, as recited in the subject claims.

Furthermore, the mere disclosure by von Borstel that uridine can be administered orally would have provided no evidence to a person of average skill in the art that orally administered uridine could be converted to cytidine in the brain, as allegedly taught by Dawson. It was well known in the art that orally administered nutrients are often not metabolized in the same manner as nutrients that are subcutaneously injected, the method utilized by Dawson. Thus, von Borstel did not even show that orally administered uridine could be converted to cytidine in the brain, much less so that it would increase brain cytidine levels. In the absence of any evidence that orally administered uridine can be converted to cytidine, a person of average skill in the art would not have been motivated to combine the teachings of von Borstel with either Dawson or Lehninger to practice a method of increasing brain cytidine levels, comprising orally administering a uridine, as recited in claim 55 of the subject application.

Similarly, the mere disclosure by von Borstel that uridine monophosphate can be administered would have provided no evidence to a person of average skill in the art that uridine monophosphate could be converted to cytidine in the brain. In the absence of any evidence that uridine monophosphate can be converted to cytidine, a person of average skill in the art would not have been motivated to combine von Borstel with either Dawson or Lehninger to practice a method of increasing brain cytidine levels, comprising administering uridine monophosphate, as recited in claims 58 and 61 of the subject application.

In addition, von Borstel did not show that administration of uridine in a uridine-rich food could be converted to cytidine in the brain, as recited in amended claim 57. In fact, von

APPLICANT(S): WURTMAN, Richard  
SERIAL NO.: 09/363,748  
FILED: June 30, 1999  
Page 8

Borstel does not mention or even suggest the use of a uridine-rich food to administer uridine. In the absence of any evidence that uridine in a uridine-rich food can be converted to cytidine, a person of average skill in the art would not have been motivated to combine the teachings of von Borstel with either Dawson or Lehninger to practice a method of increasing brain cytidine levels, comprising administering uridine in a uridine-rich food, as recited in claim 57.

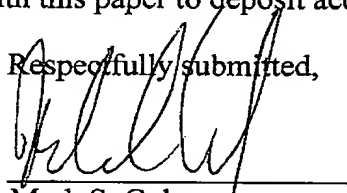
Accordingly, Applicants request withdrawal of the rejections.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3335.

Respectfully submitted,



Mark S. Cohen  
Attorney for Applicant(s)  
Registration No. 42,425

Dated: March 1, 2005

**Pearl Cohen Zedek Latzer, LLP**  
10 Rockefeller Plaza, Suite 1001  
New York, New York 10020  
Tel: (212) 632-3480  
Fax: (212) 632-3489